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Research paper

Clinical trials supported by the Tinnitus Research Consortium: Lessons learned, the Southern Illinois University experience

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ABSTRACT

The Tinnitus Research Consortium funded three clinical trials investigating treatments for chronic bothersome tinnitus at Southern Illinois University School of Medicine. The trials were designed to measure the subjective changes in tinnitus distress using standardized questionnaires and objective changes in tinnitus loudness using psychophysical matching procedures. The results of the first two trials have been published and are summarized here. The first trial investigated the effect of gabapentin on the loudness and annoyance of tinnitus in adults with chronic bothersome tinnitus with and without a history of acoustic trauma. A small but significant number of subjects reported decreased tinnitus annoyance that corresponded with a decrease in objective measures of tinnitus loudness during active drug treatment with a washout effect during placebo treatment. The second trial compared the effect of tinnitus retraining therapy (TRT) on adults with normal to near-normal hearing and chronic bothersome tinnitus to treatment with general counseling without acoustic enrichment. Significant improvements in tinnitus severity, but not in objective psychometric measures of tinnitus loudness, occurred in both treatment groups, however a greater effect was observed in the TRT group compared with the control group. The third trial is nearing completion and investigates the long-term results of tinnitus retraining therapy on chronic bothersome tinnitus in adults with hearing loss. Significant lessons and observations on conducting tinnitus clinical trials were learned from these three trials. The challenges of recruiting and retaining study participants is discussed. More importantly, the reliability and stability of the Tinnitus Handicap Inventory (THI) over long intervals is presented. The implications of this variability for the design and interpretation of future tinnitus studies is discussed.

This article is part of a Special Issue entitled <Tinnitus>.

The design and deployment of clinical trials investigating tinnitus presents many challenges. Not the least of these is the availability of funds to conduct trials and the engagement of well-informed reviewers vetting applications. The Tinnitus Research Consortium (TRC) was a unique and ground-breaking answer to these challenges and was instrumental in moving forward the clinical and basic research of tinnitus. Prior to the TRC, progress and interest in tinnitus research (as evidenced by publications, available funding, promising theories and hypotheses) was sparse. In 1998 the first request for applications from the TRC was announced, a critical point in the field of tinnitus research.

The TRC funded three clinical trials at Southern Illinois University School of Medicine. The first trial studied the effect of gabapentin on the sensory features and subjective impact of chronic tinnitus (Bauer and Brozoski, 2006). The second and third trials investigated the efficacy of Tinnitus Retraining Therapy (TRT) on sensory features and impact of chronic tinnitus. The second (Bauer and Brozoski, 2011) and third trials, the latter nearing completion, were among the first controlled trials in non-military personnel investigating the effect of acoustic therapy, in the context of TRT, on tinnitus management. Both trials were designed to detect a significant and meaningful clinical difference in long-term tinnitus improvement. In this article, the design and results of our TRC funded trials are reviewed, ending with a brief summary of the lessons learned from these endeavors. All our studies were approved by the Springfield Committee for Research in Human Subjects (SCRIHS) and listed on the national registry ClinicalTrials.gov.

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1. Gabapentin and tinnitus

Our motivation in 2002 to conduct a clinical trial investigating the effect of gabapentin, a gamma-amino butyric acid (GABA) analog, on chronic tinnitus was derived in part from animal model research (Bauer and Brozoski, 2001) as well as knowledge of pathologic changes known to occur in the central auditory pathway in response to auditory trauma (Bauer and Brozoski, 2007). There was ample evidence that hearing loss, secondary to aging (Caspary et al., 1995) and acoustic trauma (Brozoski et al., 2012; Wang et al., 2011) triggered significant changes in inhibitory neurotransmitters throughout the auditory pathway. Animal studies using an operant conditioned-suppression psychophysical method, in rats and chinchillas, demonstrated long-term evidence of tinnitus after unilateral acoustic trauma (Brozoski and Bauer, 2008). The behavioral expression of tinnitus in animals was accompanied by loss of inhibition as reflected in enhanced neural activity at multiple sites within the auditory brainstem and midbrain (Bauer et al., 2006; 2013; Brozoski et al., 2002; Wang et al., 2011). Most intriguing was the finding that the behavioral evidence of acoustic-trauma-induced tinnitus was partially reversed with gabapentin (Bauer and Brozoski, 2001), a drug approved for treatment of seizure disorders. The effect of an indirect GABA agonist, vigabatrin, as well as a direct extra-synaptic GABA agonist, taurine, later confirmed that enhanced GABA inhibition decreased the perception of tinnitus in animals (Brozoski et al., 2007, 2010). Case reports (Zapp, 2001) and a small clinical case series (Shulman et al., 2002) documented the improvement in tinnitus in people receiving gabapentin. These results were intriguing but the lack of controlled assessment suggested, at best, cautious optimism that a potentially effective pharmacologic treatment of tinnitus was at hand.

Design of the gabapentin trial funded by the TRC was directly informed by animal studies we had conducted (Bauer and Brozoski, 2001). It had been hypothesized that more than one mechanism causes tinnitus, and that each pathophysiologic mechanism may derive from a specific type of auditory system insult (Hoffman and Reed, 2004). If true, then one would not expect a uniform response to a drug treatment administered to a random sample from the clinical population. Rather, drug efficacy might be optimum for a subpopulation characterized by a specific pathological condition. Information on an optimum gabapentin dose for tinnitus was also an unknown. These considerations led to the study design investigating a broad range of gabapentin doses on subjects with tinnitus attributed to high-level sound exposure, as well as on subjects with tinnitus not attributable to sound exposure. The latter group would serve as an active control. The rationale was derived from the preceding gabapentin animal studies, where tinnitus was induced with sound exposure resulting in a modest permanent threshold shift. The clinical trial design also addressed the potential of a placebo effect. Placebo effects are well-recognized in all clinical trials, and they particularly pose an issue in studies of tinnitus treatments (Duckert and Rees, 1984). The drug dose regimen, therefore, included both entry and washout placebo phases, bracketing escalating (800 mg, 1800 mg and 2400 mg) and decreasing drug dose (900 mg) series, with each dose level tested for three to four weeks. Participants were blinded with respect to dose. Assessment at the conclusion of each placebo and drug dose period was standardized using automated computer-based routines, psychophysical assessment of tinnitus loudness, a standardized questionnaire of tinnitus impact, the Tinnitus Handicap Questionnaire (THQ), and a set of 7 scaled questions regarding the subjective sensory features of tinnitus, the Tinnitus Experience Questionnaire (TEQ). To summarize, salient features of this study were, inclusion of multiple subjective and objective measures of tinnitus, multiple drug dose levels given to all subjects with blinded testing for each dose level, the segregation of experimental groups based on tinnitus etiology, with a specific attempt to include an etiology likely to show an effect (history of acoustic trauma) and one unlikely to show an effect (tinnitus without acoustic trauma).

The results of the study were informative in several ways. First, the study established the limited efficacy of gabapentin in decreasing the loudness and impact of tinnitus. Although there were subjects with significant improvement in objective measures of tinnitus loudness, and corresponding improvement in standardized questionnaire assessment of tinnitus impact, these responders comprised a minority: six of twenty subjects with noise-exposure history, and four of nineteen without a history of noise exposure. We observed significant variability in the optimum effective drug dose between individuals, with a range in daily dose between 800 mg and 2400 mg. The objective psychometric measurement of tinnitus loudness, using a multiple-stimulus loudness matching procedure, was also informative. The objective measure of loudness paralleled the subjective (i.e., questionnaire based) measures of loudness and annoyance related to tinnitus. The parallel improvement in tinnitus impact and tinnitus loudness documented with subjective and objective measures suggested that drug efficacy, when evident, occurred via a mechanism that involved neural pathways relevant to sound perception. This helped to clarify a putative mechanism of gabapentin therapy for tinnitus. Gabapentin treatment appears to primarily impact the sensory features of tinnitus (i.e. loudness), and this has a positive impact secondarily on the higher-order non-sensory features of tinnitus such as attention, emotion, and cognition.

Gabapentin is arguably one of the few medications studied in a series of trials for efficacy in tinnitus management. As such, it is of interest to examine the results of these trials and the possible reasons for failure to replicate. Three other studies investigated the utility of gabapentin as a tinnitus modulator, with mixed effects noted in each. All were placebo-controlled trials showing some efficacy of the drug in specific subpopulations. The first enrolled 76 adults with tinnitus of at least 3 months duration, randomized to receive a target dose of 600 mg three times a day or placebo, with assessments at baseline, week 1 (gabapentin 300 mg daily), week 5 (after a two week period on the target dose) and after a washout phase at week 9 (Witsell et al., 2007). There was no difference in the primary outcome measure, the Tinnitus Handicap Inventory (THI), at any time point for either the drug or placebo group. There was, however, a difference in the secondary outcome measure, a rating of global tinnitus severity. A significantly greater number of subjects treated with gabapentin (37.5%) reported overall improvement in their tinnitus compared with control subjects receiving placebo (6.7%; $p < 0.026$). Factors that might have contributed to the improvement, such as improved sleep, improved mood, or decreased loudness of tinnitus, were not explored.

A study by Piccirillo et al. (2007) evaluated the effect of gabapentin on adults with moderate to severely disturbing tinnitus of at least 6 months duration. Subjects were randomized to either a placebo group or a gabapentin group, with a target treatment dose of 3600 mg a day for a fixed period of four weeks. A modified intention-to-treat analysis was performed that included subjects receiving only one dose during the fixed dose period. There were two notable outcomes. First, in subjects with normal hearing, there was a significant improvement in the primary outcome measure (total THI score) in the Gabapentin group compared with placebo ($p = 0.005$). Second, there was a significant difference between treatment groups and assessments periods, within the included three age strata (18–53, 54–59, and 60–70; $p = 0.04$). The definition of normal hearing used in the study was not given, but it would be interesting to know if these subjects had audiometric evidence of noise induced hearing loss.